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A prospective study of levetiracetam efficacy in epileptic syndromes with continuous spikes-waves during slow sleep

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ABSTRACT

Purpose: To evaluate the add-on effect of levetiracetam (LEV) treatment on the EEG and clinical status of children with continuous spikes-waves during slow sleep (CSWS).
Methods: 20 children with CSWS refractory to other conventional antiepileptic drugs (AEDs) received LEV 45–50 mg/kg/day as add-on treatment, and were prospectively followed for a minimum period of 18 months. The patient population comprised seven cryptogenic, seven symptomatic and six idiopathic cases (atypical benign partial epilepsy, aBECTs). The electrographic evaluation included 24 h EEG recordings taken every six months (minimum of three per child). Electrographically children were categorised as responders, partial responders or non-responders by comparing changes in the spike index (SI) during NREM-sleep with baseline SI before initiation of LEV. The clinical efficacy of LEV was assessed by comparing seizure frequency at the end of follow up with the baseline. The follow up duration varied from 18 to 53 months.
Results: Electrographic response was observed in 11 patients. Eight patients demonstrated a lasing response (more than 12 months): five from symptomatic, two – cryptogenic and one – idiopathic group respectively. Three children showed a partial response (6–12 months): one from symptomatic and two from idiopathic group.

Eleven out of the 20 children were seizure free at baseline and during the whole follow up. The rest, six-symptomatic and three-cryptogenic patients, had seizures prior to LEV treatment initiation. Six became seizure free after add-on therapy with LEV, and in three children a significant reduction of seizure frequency was observed.
Conclusion: This study suggests that add-on therapy with LEV is more effective in children with CSWS resulting from a known underlying structural brain lesion (the symptomatic group).

1. Introduction

Epileptic syndromes with continuous spikes-waves during sleep represent a wide spectrum of epileptic conditions which have CSWS as a common specific EEG-feature. These conditions are of variable severity, duration and outcome. During the period when spike-wave activity during sleep dominates the EEG record, a marked decrease in performance is usually observed, and can include impairment of cognitive, language, motor or behavioural functions.[1]

The mechanisms underlying these neuropsychological disturbances have yet to be clarified. Many studies have attempted to correlate the amount of spike-wave activity under sleep with the clinical impairment observed in these children. The presence of CSWS on the EEG is almost certainly enough for the appearance of cognitive impairments.[2] Evidence suggests that suppression of this epileptic activity can quite dramatically improve these functions.[2,3]

Successful treatment of epileptic syndromes with CSWS has always been problematic, usually offering little or no respite from symptoms, or at best, a transitory response.[4] The most commonly used drugs are sodium valproate, benzodiazepines, ethosuximide, sultiame and steroids.[1,5–8] However there is no general agreement, whether steroids or antiepileptic drugs should be used as a first choice medication, or on the duration of treatment after reaching clinical and electrographic improvement. During recent years the potential efficacy of some new antiepileptic drugs, such as lamotrigine, topiramate, and, especially, levetiracetam, has been demonstrated in the treatment of CSWS.[9–12] LEV is a water soluble pyrrolidine derivative and an analogue of piracetam. The efficacy of LEV as an add-on medication in focal epilepsies has been well documented.[13] However, the mode of action of LEV is not

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completely understood.[14] LEV may act by selectively preventing hypersynchronisation of epileptiform burst firing, thus inhibiting the spread of spike activity.[15] Recently the synaptic vesicle protein SV2A, has been suggested as a possible binding site for LEV.[14] A beneficial effect of LEV in epileptic syndromes with CSWS has been reported by several investigators.[11,12,16,17] However these reports have either evaluated a small number of children or followed them during a short period.

We report on a larger prospective study carried out over a longer period of time; 20 children were evaluated during a period of 18–53 months.

2. Patients and methods

We studied 20 children (fourteen boys and six girls) aged between four and thirteen years with CSWS resulting from various aetiologies: six cases were idiopathic, seven – cryptogenic and seven – symptomatic. Age at CSWS detection varied from five to ten years, CSWS duration – from five to 50 months (Table 1). In all patients the efficacy of the consecutive treatment with the conventional AEDs (sodium valproate, benzodiazepines, ethosuximide, sultiame) was lacking in terms of EEG features and neuropsychological characteristics. Eleven out of 20 children were seizure-free before LEV introduction.

Before initiation of LEV therapy all patients underwent magnetic resonance imaging (MRI), 24-h EEG recording and neuropsychological testing using Wechsler Intelligence Scale for Children III (WISC-III) and Wechsler Preschool and Primary Scale of Intelligence Revised (WPPSI-R). In 4 children the Leiter International Performance Scale was used because of severe cognitive deterioration and lack of the ability to cooperate with verbal tasks. The assessment of cognitive development was based on the full IQ (intelligence quotient) scores: 80–100, normal, 60–80, mild delay, 50–60, moderate delay and <50, severe delay.

LEV was administered as add-on therapy at the doses 45–50 mg/kg/day. All concomitant AEDs remained unchanged. The clinical efficacy of LEV treatment was evaluated by comparing the seizure frequency at the end of follow up with the baseline. The follow up period comprised 18–53 months.

Table 1
Patient clinical characteristics.

Total number	$n=20$
Gender	
Male	14
Female	6
Age (years)	
Range	4–13
Epilepsy syndrome diagnosis	
aBECTs	6
Epilepsy with CSWS	7
Symptomatic focal epilepsy	7
CSWS aetiology	
Idiopathic	6
Cryptogenic	7
Symptomatic:	7
Hypoxic–ischemic encephalopathy	3
Focal polymicrogyria	2
Partial trisomy 13/21	1
Age at CSWS onset (years)	
Range	5–10
CSWS duration (months)	
Range	5–50
Concomitant AEDs[a]	
VPA	4
STM	5
VPA + CLB	3
VPA + STM	2
STM + CLB	4
STM + LTG	1
VPA + ESM	1

[a] VPAL: valproate; S^{TM}: sultiame; CLB: clobazam; LTG: lamotrigine; ESM: ethosuximide.

2.1. Electrographic criteria for CSWS

The accepted morphology for epileptiform activity was a spike (duration between 20 and 70 ms) followed by a slow wave, with a frequency between 1 and 4 Hz. All children in the study had at least one recording where the percentage of epileptic discharges in NREM-sleep exceeded 80%.

2.2. Quantification of epileptiform activity during sleep

The percentage of epileptiform activity occurring during sleep can be expressed as the spike index (SI). The method of arriving at the SI varies from centre to centre. In our centre we use a semi automatic quantification method based on spike-detection, using patient specific template matching. The percentage is calculated using the sum of the periods of NREM-sleep during the whole night.[18]

Electrographic data for each child was collected over a minimum period of 18 months, and for many patients, considerably longer (Tables 2 and 3). The qualitative data (Table 2) included presence of background slowing on the EEG, the regional location of the predominant spike-wave activity in wakefulness and sleep. The mode of distribution of spike-wave activity during sleep was considered either regional, defined as consistently occurring over one location/region without spread to the contra-lateral hemisphere, or focal with secondary bilateral synchrony (SBS), as defined by Blume and Pillay,[19] and occurring over both hemispheres.

The quantitative data (Table 3) included: the epilepsy syndrome, the number of years with known CSWS, the baseline spike-index (BSI)-defined as the SI from the EEG control prior to the start of LEV as add-on treatment, the number of months in LEV treatment (range 18–53 months) and the last spike-index (LSI).

The difference between the BSI and the LSI was defined as the electrographic response to LEV add-on treatment, and was subsequently graded as follows:

- Responders: (Grade I) reduction in SI >50%
- Partial responders: (Grade II) reduction in SI between 25 and 50%.
- Non responders: (Grade III) reduction in SI <25% or an increase in SI.

The electrographic response was also categorised in terms of its duration. Absence of CSWS on the EEG for more than 12 months was assessed as lasting response, for 6–12 months – as partial response.

The number of patients was considered too small for statistical analysis.

3. Results

3.1. Clinical response

Eleven from 20 children were seizure-free before initiation of LEV therapy and during whole follow up. Six patients from symptomatic and three from cryptogenic group had seizures before LEV introduction. At the end of follow up six out of these nine children were seizure-free (three symptomatic, three cryptogenic), and significant reduction of seizure frequency was observed in the remaining three patients. LEV was well tolerated by all the patients.

Table 2
Electrographic characteristics: qualitative and response grade.

Patient number	Aetiology	Background slowing	Predominant paroxysmal abnormality – awake	Predominant paroxysmal abnormality – asleep	Apparent SBS or regional
1	Cryptogenic	No	Right F+pT	(R) pT+F	Regional
2	Cryptogenic	No	F/T	F->T	SBS
3	Cryptogenic	No	F/P	F	SBS
4	Cryptogenic	Yes	F/T	F->T	SBS
5	Cryptogenic	No	Right F/T	(R) F->T	SBS in periods
6	Cryptogenic	No	Left T	(L) T	SBS in periods
7	Cryptogenic	No	Left P/T+F	(L) P+F->C	SBS
8	Symptomatic	No	Left F/T	F->T	SBS
9	Symptomatic	Yes	Left F/T	F	SBS
10	Symptomatic	No	Left P/C/T	(L) P/C/T	Regional
11	Symptomatic	No	Left T/C	(L) T/C	Regional
12	Symptomatic	No	Right P/C	(R) P/C	Regional
13	Symptomatic	No	Right T/P	(R) T	SBS in periods
14	Symptomatic	Yes	Right T/P	(R) T/P	Regional
15	aBECTs	No	Right C/T/P	(R) C/T	Regional
16	aBECTs	Yes	Right P/C + Right F/T	(R) P/C (R) F/T	SBS in periods
17	aBECTs	No	Right F/T + Right T/C/P	(R) F->T (R) P/T	SBS
18	aBECTs	Yes	Right T/C	(R) T/C	Regional
19	aBECTs	Yes	Right P/T/C + Left P/T/C	(R) P/T/C (L) P/T/C	Regional
20	aBECTs	No	Right T/C/P Later F	(R) T/C/P Later F	Regional Later SBS

F: frontal; T: temporal; pT: post temporal; C: central; P: parietal.

3.2. Electrographic response

EEG response is summarized in Table 3. During NREM sleep, discharges usually show a fronto-central or fronto-temporal maximum. The general trend in our population with cryptogenic aetiology was a frontal maximum, sometimes with temporal spreading and SBS, and they did rather badly on medication. The exceptions were patients one and five, one of whom had regional spike-waves over the frontal and post temporal region, with accentuation of the post temporal discharges during sleep, and no SBS. This patient responded well to LEV treatment. Another had frontal spike-waves and occasional SBS, and also responded well to LEV treatment.

The symptomatic group had the least tendency to SBS and generally responded well to LEV treatment. Patients eight and nine had frontal spike-waves and SBS, but responded well to LEV medication. Patient 14 had two foci, one temporal, which in periods triggered SBS, but responded well to LEV medication.

In the idiopathic group three patients did not develop SBS. These patients did not usually exhibit frontal spike-waves, but tended to show a maximum in the centro-temporo-parietal regions. Patient 15 responded well to LEV treatment and patient 18 showed a partial response. Patient 16 had two foci, the frontal focus being the less dominant and occasionally triggering SBS. This patient also showed a partial response to LEV treatment.

Thus, in cryptogenic group (patients one to seven), two patients showed a lasting response, and the remaining five – no response. In symptomatic group (patients 8–14), all but one, showed improvement: five – lasting response and one – partial response. In idiopathic group (patients 15–20), a lasting response was demonstrated only in one child. Two children showed a partial response and in three no improvement was observed.

Table 3
Electrographic characteristics: quantitative and response grade.

Pt	Age, years	Gender	Aetiology	BSI	Months in LEV treatment	LSI	Response grade
1	10	F	Crypt.	48	41	No CSWS	I
2	5	F	Crypt.	Not known	53	95	III
3	8	M	Crypt.	70	33	64	III
4	6	M	Crypt.	87	47	97.	III
5	12	M	Crypt.	48	30	No CSWS	I
6	6	M	Crypt.	65	18	88	III
7	4	M	Crypt.	85	18	76	III
8	12	M	Sympt.	80	18	Norm	I
9	13	F	Sympt.	65	43	No CSWS	I
10	9	M	Sympt.	80	26	55	II
11	9	M	Sympt.	86	30	40	I
12	10	F	Sympt.	86	18	No CSWS	I
13	11	M	Sympt.	54	45	67	III
14	11	F	Sympt.	52	25	Norm	I
15	7	M	Idiopat.	80	19	No CSWS	I
16	9	F	Idiopat.	87	24	56	II
17	7	M	Idiopat.	75	32	89	III
18	4	M	Idiopat.	82	27	60	II
19	6	M	Idiopat.	46	25	46	III
20	5	M	Idiopat.	Not known	23	80	III

BSI: baseline spike-wave index; LSI: last spike-wave index. Response grade as described under Section 2.

Table 4
Cognitive development before and after LEV therapy.

Groups of patients/cognitive development	Before LEV therapy	At the end of follow-up
Idiopathic ($n=6$)		
Normal	4	1
Mild delay	1	4
Moderate delay	1	1
Severe delay	0	0
Cryptogenic ($n=7$)		
Normal	2	0
Mild delay	3	2
Moderate delay	1	2
Severe delay	1	3
Symptomatic ($n=7$)		
Normal	1	1
Mild delay	2	1
Moderate delay	1	1
Severe delay	3	4

3.3. Neuropsychological outcome

Before the initiation of LEV therapy four out of six patients in the idiopathic group had normal cognitive development, one child – mild and one – moderate delay. In the cryptogenic group two out of seven children had normal IQ scores, three – mild delay, one – moderate and one – severe delay in the cognitive development. In the symptomatic group one patient out of seven had initially normal cognitive development, two were mildly delayed, two – moderately and three – severely delayed. The neuropsychological outcome is presented in Table 4. In both idiopathic and cryptogenic groups the cognitive development declined, despite the clinical and electrographical improvement. However in symptomatic group no significant neuropsychological deterioration was observed at the end of follow-up. The duration of CSWS was the main predictor of the severity of neuropsychological outcome showing a linear correlation: the longer was the duration of CSWS, the poorer was the outcome. This data is in accordance with the other studies.[1,20,21]

4. Discussion

This is the first study showing LEV, as add-on therapy, to be effective over a long period of time in children with CSWS resulting from symptomatic epilepsy. Moreover, this study reveals only partial or no effect in the majority of cases with CSWS of other aetiologies, namely idiopathic or the classic CSWS syndrome.

A limited number of previous studies have shown LEV to be effective in CSWS resulting from various aetiologies. Kramer et al.[16] reported efficacy in seven of 17 children, the duration and relapse rate unknown. Wang et al.[17] demonstrated LEV efficacy in five of six children, but two of five responders relapsed four and five months respectively. Capovilla et al.[11] observed efficacy in two of three children, (all with symptomatic epilepsy and CSWS), followed for 15 and 12 months respectively. A partial response was recorded in the third child. Aeby et al.[12] reported improvement of the EEG in seven of 12 children after a two month period, and the neuropsychological and/or behaviour improvement in nine. In their study LEV had been discontinued after one year in four patients because of CSWS relapse. The only prospective study to date,[17] showed no response to LEV treatment in the four patients treated, their aetiologies were not specified.

In our study we report on the efficacy of LEV add-on treatment in terms of electrographic response, seizure frequency and neuropsychological outcome. The close temporal association between the epileptic discharges during sleep and the deterioration of cognitive and behavioural functions is generally accepted,[22,23] even though the mechanisms underlying these disturbances remain unclear. At this present time, the goal of treatment must be the effective reduction of epileptic discharges during sleep over as long a period as possible, if not permanently.

Some of the problems experienced in reporting on the apparent efficacy of a chosen medication in the treatment of CSWS include spontaneous recovery in some patients, transient electrographic and clinical changes that are not related to alterations in medication, and the unpredictability of relapse. We have tried to overcome these problems by evaluating children over a longer period and using fixed methods of quantitative and qualitative evaluation, at a maximum of 6 monthly intervals. Concomitant medications remained unchanged during the study.

Whilst the three epileptic syndrome groups share many similar clinical and electrographic manifestations during sleep, the response to LEV appears to differ between these groups, showing increased efficacy in the symptomatic group, as was also shown by Capovilla et al.[11]

We cannot at this time explain why this should be so, or indeed, whether it is only a chance finding.

We considered the presence of SBS, which by definition suggests a cortical site of hyperexcitability in the leading hemisphere, capable of rapid transverse of the corpus callosum. Experimental data has shown that, the burst firing pattern associated with spindling in the early sleep stages can develop into bilateral synchronous self sustaining spike-wave discharges.[24] Furthermore, this phenomenon may be age limited.[22] Related to the purpose of our study, we found that children not exhibiting SBS seemed to respond better to LEV treatment.

Secondly, we considered the location of the predominant paroxysmal activity. As reported by Blume and Pillay,[19] SBS favours a frontal location – this was a trend we found. The temporal and parietal paroxysmal locations correlated generally with a better response to LEV treatment.

5. Conclusion

LEV as an add-on treatment 45–50/mg/kg/day, would seem to be an effective and lasting treatment for children with CSWS resulting from symptomatic epilepsy, where the paroxysmal activity has a regional location without SBS. In the future, further evaluation using a larger population is required. Additionally, the mechanisms triggering SBS, and their relevance to the spread of epileptic discharges in the CSWS-syndrome require further evaluation.

Conflict of interest

None.

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